PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference POP-0007.PCT	**FOR FURTHER ACTION** See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/IB 02/05583	International filing date *(day/month/year)* 23.12.2002	Priority date *(day/month/year)* 29.12.2001
International Patent Classification (IPC) or both national classification and IPC C07K5/083		
Applicant POLYPEPTIDE LABORATORIES A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 07.07.2003	Date of completion of this report 15.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Lüdemann, S Telephone No. +49 89 2399-7842

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/05583

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-12	as published

Claims, Numbers

1-13	as published
11, 12, to delete: 2, 3	received on 03.05.2004 with letter of 29.04.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1(partially),11(complete) .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1 (partially)
	No:	Claims	11
Inventive step (IS)	Yes:	Claims	1 (partially)
	No:	Claims	11
Industrial applicability (IA)	Yes:	Claims	1 (partially), 11
	No:	Claims	-

2. Citations and explanations

   see separate sheet

The arguments of the applicant have been considered. However, the International Preliminary Examination Report has been established as if some of the amendments (claims 2-10) had not been made.

Re Item I

Basis of the report

Claims 2 and 7 are not allowable since the requirements of R. 70.2(c) are not met for the following reasons:

Claims 2 and 7 filed with the letter dated from 29.04.2004 have been made dependent on claim 1. Thus, the subject-matter of claims 2 and 7 now covers a process for preparing an LHRH antagonist, comprising steps (a)-(d) of claim 1 and a further step of coupling the tripeptide (I) to compound (IV). This more specific process covering the additional procedural features (a)-(d) of claim 1 goes beyond the content of the application as originally filed. The description on p.5, lines 19ff, discloses a general process of preparing LHRH antagonists without referring to the method of claim 1, outlined above. The objects of the invention given on p.2-3 also do not clearly teach a combination of the process of claim 1 with the process of claim 4. Since the combination of said processes can not be derived from the description, claims 3-6 and 8-10 which are dependent on claims 2 and 7 are also not allowable according to R. 70.2(c).

Therefore, claims 2-10 filed with the letter dated from 29.04.2004 have not been considered for this report.

Claims 11 and 12 filed with the letter dated from 29.04.2004 meet the requirements of R. 70.2(c). Claim 1 and the examples are considered as support for said claims.

Thus, the set of claims as originally filed, in which claims 2 and 3 (both product claims) of the originally filed version have been replaced by claims 11 and 12 (product-by-process claims) filed with the letter dated from 29.04.2004, can be seen as the basis of the present report.

Re Item IV

Lack of unity of invention

2. The present application does not meet the requirements of unity of invention and a lack of unity "a posteriori" is indicated (R. 13.1 PCT):

2.1 The separate inventions are:

2.1a Subject 1: claim 1 (partially) and (claim 2 as originally filed or) claim 11 as filed with 29.04.2004
A process for preparing the tripeptide of the formula I with the N-terminal protecting group Ac as given by claim 1 and the tripeptide according to claim 2/11.

2.1b Subject 2: claim 4 (partially) and claims 5, 7 as originally filed
A process for preparing an LHRH antagonist comprising coupling the tripeptide of formula I and the heptapeptides of formulae V and VI.

2.1c Subject 3: claim 4 (partially) and claims 6, 8 as originally filed
A process for preparing an LHRH antagonist comprising coupling the tripeptide of formula I and the heptapeptides of formulae Va and VIa.

2.1d Subject 4: claim 1 (partially) and (claim 3 as originally filed or) claim 12 as filed with 29.04.2004
A process for preparing the tripeptide of the formula IX with the N-terminal protecting group Boc as given by claim 1 and the tripeptide according to claim 3/12.

2.1e Subject 5: claim 9 (partially) and claims 10,11 as originally filed
A process for preparing an LHRH antagonist comprising coupling the tripeptide of formula IX and the heptapeptides of formulae V and VI.

2.1f Subject 6: claim 9 (partially) and claims 12,13 as originally filed
A process for preparing an LHRH antagonist comprising coupling the tripeptide of formula IX and the heptapeptides of formulae Va and VIa.

These inventions are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

2.2 The present application relates to processes for the synthesis of LHRH antagonists. The linking concept of the above listed inventions is to be seen in the provision of tripeptides with the generalised formula Q-D-2Nal-D-4ClPhe-D-3Pal-OH, with a protecting group Q (which in the present application can be Ac or Boc). Since the use of such protected tripeptides in the synthesis of LHRH antagonists is known from D1 (see e.g. claim 1), disclosing Q-D-2Nal-D-4ClPhe-D-3Pal-OH, with Q being N-acetyl (correponding to Ac in the present invention) or THF-Gly, the linking concept is not novel (confer also Item V 2.2).

2.3 Since also the heptapeptides of formula (IV) have been disclosed in D1 (see claim 1), the reactions of the tripeptide I with the different heptapeptides of the different sequences V and Va with different amino acids AA1 and AA2 are considered as further independent inventions.

2.4 The inventions 4-6 listed above are also not linked by a novel and inventive linking concept for the following reasons: The tripeptide with the formula (IX) with Boc as an N-terminal protecting group can be considered as the essential technical linking feature of inventions 4-6. The difference between tripeptide IX and the tripeptides disclosed in D1 is that the N-terminus in the present application is protected by Boc instead of Ac or THF-Gly. Therefore, the problem to be solved by inventions 4-6 is to be seen as the provision of an alternatively protected tripeptide Q-D-2Nal-D-4ClPhe-D-3Pal-OH. The solution cannot be seen as to involve an inventive step, since peptides protected by Boc at their N-terminus are well known in the art (see also oligopeptides of claim 19(v)-(19(x) in D1). Therefore, the requirement of unity of invention for the above-listed subjects 4-6 as laid down by R. 13.2 is also not fulfilled (confer also Item V 2.2).

2.5 Since the application lacks unity and the applicant has not responded to the "Invitation to restrict or pay additional fees", only the main invention will be examined as laid down by Art. 34 (3) (c) PCT. It has further been stated that invention 1 is considered as the main invention. Therefore, no opinion will be formulated with respect of claims 1 (partially), 3-13. Claim 1 will only be examined in part, i.e. a process for preparing a tripeptide of the formula (I), the second embodiment of claim 1 (corresponding to invention 4), will be excluded from examination (see lack of unity reasoning and definition of invention 4).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document:

   D1: US-A-5710246

   D1 discloses the synthesis of LHRH antagonists by the coupling of tripeptides with the formula Q-D-2Nal-D-4ClPhe-D-3Pal-OH with heptapeptides P1-Ser(P2)-NMeTyr(P3)-D-Lys(Nic)-Leu-Lys(iPr)-Pro-DAlaNH$_2$. Schemes for synthesis of the tripeptides (see Scheme III) are given and a list of possible reactions (see scheme I in col 5 and 6, and col 7 and 8) are provided and reagents such as N-hydroxysuccinimide (see col. 7, line 56) are prompted. Examples 21-31 deal with the synthesis of such tripeptides.

2.1 The subject-matter of claim 1, **as far as it regards a process for preparing a tripeptide of the formula (I)** is novel and involves an inventive step in the sense of Art. 33(2) and (3) PCT for the following reasons:

   The process is novel over D1, since the process of the present application is performed without C-terminal protection on H-D-3Pal-OH in step (b) and further on compounds (VIII) and (IX). D1 teaches a process, in which the C-terminus is protected by a protection group P^4 (see scheme III, on col. 11). D1 does not teach or suggest to perform the process without unprotected C-terminus. It further does not appear to be obvious to the person skilled in the art to perform the process without C-terminal protection and advantages of the present process have been described on p. 7, lines 19-34.

2.2 The subject-matter of (claim 2 as originally filed and) claim 11 filed on 29.04.2004 contravenes Art. 33(2) and (3) PCT for the following reasons:

   The product of (claim 2 as originally filed and) claim 11 filed on 29.04.2004 is not

novel over D1, since compound (I) has been anticipated on col. 4, lines 25-30. The substituent Q has been defined as N-acetyl on col. 4, lines 11-12.

The applicant is informed that a product defined in terms of a process of manufacture can only be considered as novel and inventive if the **product as such** fulfills the requirements of Art. 33(2) and 33(3) PCT.